

REMARKS

Claims 1-37 and 45-49 are pending in the instant application. Claims 1-29 are withdrawn due to a restriction requirement made on December 11, 2003. Applicants respectfully submit that claim 37 was also withdrawn due to the same restriction requirement, although this claim was not noted as such on the Detail Action Summary Sheet, presumably in error. Claims 30-36 and 45-49 stand rejected. Claims 30-32 and 35-36 are objected to for depending from non-elected claims 25, 15, and 1. Claim 45 is objected to for a typographical error. Applicants have cancelled claims 30-36 and 46 herein. Applicants have amended claim 45. Claims 47-49 are amended herein to depend from claims other than 46. Applicants have added new claims 50 and 51 herein. Support for new claims 50-51 and amended claim 45 can be found at page 3, lines 14- 20 and lines 24 -31, page 6, line 21 through page 7, line 10, at page 8, lines 18-29, page 10, lines 10-15 and page 11, lines 27-32 of the specification as well as throughout the examples. Thus, no new matter is added.

Information Disclosure Statement

The Examiner indicated in the Office Action that no copy of the King, *et al.* reference could be found with the parent case. Applicants herein submit a copy of this reference with a clean copy of the PTO forms 1449 from the parent case for the Examiner's consideration. Applicants have updated the serial number and attorney docket information on these forms. In addition, Applicants also include an additional PTO form 1449 with three additional references as follows:

Bailey, et al., "Cloning a *Streptomyces clavuligerus* Genetic Locus Involved in Clavulanic Acid Biosynthesis". *Biotechnology*, September 1984.

Jensen, et al., "Extending the β -Lactam Biosynthetic Gene Cluster in *Streptomyces clavuligerus*". *Industrial Microorganisms – Basic and Applied Molecular Genetics*, Chapter 22, pp. 169-176 (1993)

Mosher, et al., "Genes Specific for the Biosynthesis of Clavam Metabolites Antipodal to Clavulanic Acid are Clustered with the Gene for Clavaminate Synthase 1 in *Streptomyces clavuligerus*". *Antimicrobial Agents and Chemotherapy*, 43(5): 1215-1224 (1999).

Compliance with Sequence Rules

The Examiner requests a statement from Applicants that the computer readable sequence listing transferred from the parent and the separately filed paper copy are the same. Applicants herein submit such a statement for the file herewith.

In addition, the Examiner notes that the amino acid sequences in Figures 1A-1P are disclosed without benefit of SEQ ID NOs. The Examiner requests that these sequences be described either directly in the Drawings or in the Brief Description of the Drawings by SEQ ID NO. Applicants have amended the specification herein to include SEQ ID NOs. with a Brief Description of the Drawings at page 2 of the application. All of these sequences are disclosed in Figure 1, see discussion below, thus, no new matter is added.

Applicants respectfully submit that SEQ ID NO:1 is a 7.193kb single-stranded DNA sequence. This sequence corresponds to the DNA presented in Figure 1 of the specification, as filed, which was given as a collection of 4 overlapping fragments. Because the coding regions are to be found on both strands of the DNA, as described in the specification, the sequence in Figure 1 switches between strands, according to where the coding regions are. Therefore, there is no single strand of sequence in Figure 1 that goes all the way from 1 to 7193. The sequence listing provided includes a single complete strand covering the entire 7.193 kb sequence using the complementarity rules (Watson Crick base pairing) in order to fill in the gaps on one strand. The Applicants wish to point out that this has not resulted in any added matter since these rules of complementarity between DNA strands in a double helix are very well known in the art. In addition,

Applicants have provided sequence identifiers for the polypeptide sequences provided in Figure 1 in the sequence listing.

Objections to the Specification

The Examiner objects to the current title of the Application. Applications have herein replaced the title of the application with a new title.

The Examiner objects to the Abstract for not completely describing the disclosed subject matter. Applicants herein submit a new Abstract.

The Examiner also objects to the specification for lacking updated continuity data in the first paragraph. Applicants herein amend the specification to update continuity data.

The Examiner also objects to the specification for containing figures on pages 13-29. These pages are herein deleted.

The Examiner also objects to the specification for omitting a Brief Description of the Drawings. This description is now added to the specification at page 2. Support for this amendment can be found in the title of Figure 1 originally submitted as well as page 12, lines 6-14 of the specification.

Applicants herein submit a replacement sequence listing.

Claim Objections

The Examiner objects to 30-32 and 35-36 for depending from non-elected claims 25, 15, and 1. Claims 30-36 are cancelled herein, thus rendering the objection to these claims moot.

Claim 45 is objected to for a typographical error. The term “alenyl” is replaced with the term “alanyl” herein. Applicants respectfully request that objection to this claim be withdrawn.

35 U.S.C. § 112, second paragraph

Claims 30-32 and 35-36 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner alleges that in claim 1 genes that are “specific for 5S clavam biosynthesis in *S. clavuligerus*” that are “not essential for 5R clavam biosynthesis” are unclear. The Examiner goes on to allege that the specification teaches six genes in this category. The Examiner also alleges that in claim 15, “manipulation” and “its inclusion” are unclear terms. The Examiner also alleges that the term “low” in claim 25 is unclear. Claims 30-36 are cancelled herein, thus, rendering rejection of these claims moot.

Claims 45 and 47-49 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. In particular, the Examiner alleges that the SEQ ID NOs recited within claim 45 are found only in *S. clavuligerus*. Applicants have amended claim 45 herein to recite *S. clavuligerus* instead of *streptomyces*. Applicants have also cancelled claim 46 herein and amended claims 47-49 to depend, either directly or indirectly, from amended claim 45. Support for amended claim 45 can be found at page 6, lines 21-31 through page 7, lines 1-10 as well as throughout the examples.

Claims 31, 33, and 34 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite. Particularly, the Examiner alleges that the term “free of any 5S clavam” is unclear, alleging the word “free” is a relative term. Applicants have cancelled claims 30-36, thus making a rejection of claims 31, 33, and 34 moot. Applicants have added new claims 50 and 51 herein, which recite *Streptomyces* culture media that is free of 5S clavams “as measured by HPLC.” Support for both new claims 50 and 51 can be

found at page 8, lines 18-29, page 10, lines 10-15 and page 11, lines 27-32 of the specification.

Claims 45-49 also stand rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite. Specifically, the Examiner alleges that it is “confusing how the method steps could be carried out with genes other than those in *S. clavuligerus*.” Applicants have amended claim 45 herein to recite *S. clavuligerus* rather than any *Streptomyces*. Applicants have also cancelled claim 46 and amended claims 47-49 to depend either directly or indirectly from claim 45.

35 U.S.C. § 112, first paragraph

Claims 45-49 stand rejected under 35 U.S.C. § 112, first paragraph. The Examiner alleges that “no support is found for disrupting orfup2 and orfup3 in *S. clavuligerus* to produce clavulanic acid.” Additionally, the Examiner alleges that “degenerate variants” is not presented in the specification as originally filed. Applicants have amended claim 45 to remove orfup2 and orfup3 from its recitation. Applicants have also amended claim 45 to remove “degenerate variants of the open reading frames.” Applicants have herein also amended the Markush group contained within claim 45 to the proper format by replacing “or” with “and.”

Claims 30-32 and 35-36 are rejected under 35 U.S.C. § 112, first paragraph. Claims 30-36 are cancelled herein, thus, rendering rejection of these claims moot.

35 U.S.C. § 101

Claim 30 stands rejected under 35 U.S.C. § 101. The Examiner alleges that claim 30 does not sufficiently distinguish over clavulanic acid as it is naturally found in host cells. Applicants respectfully submit that claim 30 is cancelled herein, thus, rendering rejection of this claim moot. Applicants have added new claims 50 and 51 which are directed to “*Streptomyces* culture media” comprising clavulanic acid and free of 5S

clavams. Thus, Applicants respectfully submit that claims 50 and 51 are directed to statutory subject matter.

35 U.S.C. § 102

Claims 30-36 and 45-49 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Fleming, *et al.* (USPN 4,367,175). Specifically, the Examiner alleges that “the claims are drawn to clavulanic acid optionally that is free from clavam-2-carboxylate (C2C), 2-hydroxymethylclavam (2HMC), and 2-(3-alanyl)clavam (AC) or optionally potassium salt or optionally in combination with amoxicillin; while numerous limitation are in the claims to describe the process by which the is claimed product can be obtained, this same product, even having been obtained by other means, still anticipated the claimed invention.”

Applicants respectfully submit that a single prior art reference anticipates a claimed invention only if it identically shows every element of the claimed invention. *In re Bond*, 15 U.S.P.Q.2d 1566 (Fed. Cir. 1990). The Examiner alleges that Fleming, *et al.* teach method of purifying clavulanic acid from “fermentation of *S. clavuligerus*; said purification includes a charcoal column followed by extractions with butan-1-ol, 72% aqueous phenol/N,N-dimethylaniline/carbon tetrachloride, and barium sulphate. The final product was then tested using optical rotation, UV spectrum, IP and NMR spectrum, TLC and paper ionophoresis.” The Examiner alleges that the IR, NMR and elemental analysis showed “no signs of impurities.”

Applicants respectfully disagree that Fleming, *et al.* disclose clavulanic acid with “no signs of impurities.” Although Fleming, *et al.* describe the purity of clavulanic acid by various detection methods, they do not disclose that the substance is 100% pure, or that it shows no signs of impurities. However, Applicants have cancelled claims 30-36 herein, thus, rendering rejection of these claims moot. Applicants respectfully submit that new

claims 50 and 51 are directed to “*Streptomyces* culture media” comprising clavulanic acid and free of 5S clavams. As Fleming, *et al.* does not disclose culture medium free of 5S clavams, they do not disclose each and every element of claims 50 and 51.

Similarly, with respect to Woroniecki, *et al.* the Examiner alleges that all of Compound I is converted to compound A, clavulanic acid, in the disclosed procedure of Example 33. The Examiner goes on to allege that “the enzyme purification steps of ammonium precipitation, pellet suspension, and dialysis, no small molecule impurities from the *S. claviger* are retained.” Applicants respectfully submit that Woroniecki, *et al.* do not disclose culture medium that is free of 5S clavams. Thus, Woroniecki, *et al.* do not disclose each and every element of new claims 50-51.

With respect to claims 45-49, these claims are directed to pharmaceutical compositions. Applicants respectfully submit that Fleming, *et al.* does not disclose a pharmaceutical composition comprising clavulanic acid and free of 5S clavams. Similarly, Woroniecki, *et al.* do not disclose pharmaceutical compositions that are free of 5S clavams. Thus, neither Fleming, *et al.* nor Woroniecki, *et al.* teach each and every element of claims 45-49. Claim 46 is cancelled herein, thus rendering rejection of this claim moot.

35 U.S.C. § 103

Claims 35, 36, 48, and 49 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Woroniecki, *et al.* (USPN 5,130,241) in view of Fleming, *et al.* (USPN 4,467,175). The Examiner alleges that the instant claims are drawn to clavulanic acid that is free from the clavam-2-carboxylate, 2-hydroxymethylclavam, and 2-3(3-alanyl)clavam, in combination with amoxycillin.

Applicant respectfully submits that for a proper obviousness rejection under 35 U.S.C. § 103, the Examiner has the burden of establishing *prima facie* with evidence or

reasons that, *inter alia*, at the time of the invention, (1) the prior art of record would have suggested or motivated one of ordinary skill in the art to carry out the combination and modification of the prior art as suggested by the Examiner to arrive at the claimed invention, and (2) "the prior art would also have revealed that in so making or carrying out, those of ordinary skill in the art would have a reasonable expectation of success. Both the suggestion [or motivation] and the reasonable expectation of success must be founded in the prior art, not in the appellants' disclosure." *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991) (citations omitted).

Claims 35 and 36 have been cancelled in the instant application, thus rendering rejection of these claims moot. Applicants respectfully submit that as the Examiner concedes Woroniecki, *et al.* do not propose the combination of clavulanic acid in combination with beta-lactam antibiotics. Applicants also submit that Fleming, *et al.* do not teach or suggest that clavulanic acid is 100% pure. More importantly Fleming, *et al.* do not teach or suggest a pharmaceutical composition that is free of 5S clavams, in particular, as the Applicants instantly claim. Fleming, *et al.* teach only removing impurities in general from clavulanic acid, obtained from *S. clavuligerus*. They do not indicate that the clavulanic acid is free from 5S clavams. Thus, neither Woroniecki, *et al.* nor Fleming, *et al.* teach or suggest a pharmaceutical composition free from 5S clavams. Furthermore, as the Examiner has indicated, both Woroniecki, *et al.* and Fleming, *et al.* are directed to purification of clavulanic acid. Neither reference provides the skilled artisan with a reasonable expectation of success in making a pharmaceutical composition that is free of 5S clavams, particularly, which may also comprise beta-lactam antibiotics. Thus, the Examiner has not met either prong of the burden for establishing *prima facie* obviousness under 35 U.S.C. § 103.

Applicant respectfully submits that in view of the forgoing amendments and remarks, they have overcome the Examiner's rejection of claims 48 and 49 under 35 U.S.C. § 103. Reconsideration and withdrawal of these rejections is respectfully requested.

New Claims

Applicants add new claims 50 and 51 herein, which recite "Streptomyces culture media" comprising clavulanic acid and free of 5S clavams. Support for new claims 50 and 51 can be found at page 3, lines 14- 20, page 8, lines 18-29, page 10, lines 10-15 and page 11, lines 27-32 of the specification as well as throughout the examples.

Applicants reserve the right to prosecute, in one or more patent applications, the claims to non-elected inventions, the cancelled claims, the claims as originally filed, and any other claims supported by the specification. Applicants thank the Examiner for the Office Action and believe this response to be a full and complete response to such Office Action. Accordingly, favorable reconsideration and allowance of the pending claims is earnestly solicited. If it would expedite the prosecution of this application, the Examiner is invited to confer with the Applicants' undersigned attorney.

Respectfully submitted,



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